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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/524,837	06/15/2012	Antonio J. Grillo-López	P04644-US-5	8212

9157 7590 08/28/2019

GENENTECH, INC.
1 DNA WAY
SOUTH SAN FRANCISCO, CA 94080

EXAMINER	
KOLKER, DANIEL E	

ART UNIT	PAPER NUMBER
1644	

NOTIFICATION DATE	DELIVERY MODE
08/28/2019	ELECTRONIC

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte ANTONIO J. GRILLO-LOPEZ[1]

Appeal 2018-006082
Application 13/524,837
Technology Center 1600

Before JEFFREY N. FREDMAN, TAWEN CHANG, and DAVID COTTA, *Administrative Patent Judges*.

CHANG, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134(a) involving claims to a method of treating patients with relapsed low grade or follicular lymphoma, which have been rejected as anticipated and obvious. We have jurisdiction under 35 U.S.C. § 6(b).

We AFFIRM, but designate our affirmance as a new ground of rejection.

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[1] Appellant identifies the Real Party in Interest as Biogen Inc. (Appeal Br. 3.)

STATEMENT OF THE CASE

"The invention relates to the use of anti-CD20 antibodies or fragments thereof in the treatment of B-cell lymphomas, particularly the use of such antibodies and fragments in combined therapeutic regimens." (Spec. 1:14–16.)

Claims 15–17 are on appeal and reproduced below:

15. A method of treating patients with relapsed low grade or follicular lymphoma comprising administering rituximab at a dose of 375mg/m^2 intravenously once weekly for a total of four infusions administered on days 1, 8, 15, and 22, wherein the initial infusion rate is 50 mg/h on day 1**,** and the initial infusion rate on days 8, 15, and 22 is faster than 50 mg/h if no toxicity was seen during the infusion on day 1.

16. A method of treating patients with relapsed low grade or follicular lymphoma comprising administering rituximab at a dose of 375mg/m^2 intravenously once weekly for a total of four infusions administered on days 1, 8, 15, and 22, wherein the initial infusion rate is 50 mg/h on day 1, and the initial infusion rate on days 8, 15, and 22 is faster than 50 mg/h if no toxicity was seen during the infusion on day 1, and wherein infusions are interrupted if an adverse event occurs and resumed once the adverse event subsides.

17. A method of treating patients with relapsed low grade or follicular lymphoma comprising administering chimeric anti-CD20 monoclonal antibody at a dose of 375mg/m^2 intravenously once weekly for a total of four infusions administered on days 1, 8, 15, and 22, wherein the initial infusion rate is 50 mg/h on day 1, and the initial infusion rate on days 8, 15, and 22 is faster than 50 mg/h if no toxicity was seen during the infusion on day 1, and wherein infusions are interrupted if an adverse event occurs and resumed once the adverse event subsides, and wherein the chimeric anti-CD20 comprises a light chain variable region comprising the amino acid sequence in SEQ ID NO: 1 and a heavy chain variable

> region comprising the amino acid sequence in SEQ ID NO: 2, and human gamma 1 heavy-chain and kappa light-chain constant region sequences.

(Appeal Br. 26–27 (Claims App.).)

The Examiner rejects claims 15–17 under pre-AIA 35 U.S.C. § 102(b) as being anticipated by the prescribing information for RITUXAN®, dated November 1997. (Ans. 5.)

The Examiner rejects claims 15–17 under pre-AIA 35 U.S.C. § 103(a) as being unpatentable over the public hearing transcript of the nineteenth meeting of the Biological Response Modifiers Advisory Committee, which is a part of the Food and Drug Administration's Center for Biological Evaluation and Research, held on July 25, 1997 (hereinafter "FDA Transcript"). (*Id.*)

I.

Issue

The Examiner has rejected claims 15–17 as anticipated by the November 1997 prescribing information for RITUXAN®, a brand name under which rituximab is sold. The Examiner finds that the claimed invention are only entitled to priority to the filing date of the instant application, June 15, 2012, because "the scope of the inventions of claims 15–17 are not disclosed in the parents applications to which priority is claimed." (Ans. 3.) The Examiner finds that the November 1997 prescribing information for RITUXAN® discloses the methods of claims 15–17. (*Id.*)

Appellant does not dispute that the November 1997 prescribing information for RITUXAN® discloses the methods of claims 15–17.

However, Appellant contends that the claims are entitled to the priority date of August 11, 1998 and that the November 1997 prescribing information is thus not prior art under 35 U.S.C. § 102(b). Appellant further contends that the Grillo-Lopez Declaration[2] effectively establishes that the invention antedates November 1997 under 37 C.F.R. § 1.131, and that the prescribing information is therefore also not prior art under 35 U.S.C. § 102(a).

The issues with respect to this rejection are (1) whether the instant application is entitled to the priority date of August 11, 1998 and, if so, (2) whether the Grillo-Lopez Declaration establishes that the invention antedates the November 1997 prescribing information for RITUXAN®.

Analysis

Pre-AIA 35 U.S.C. § 102(b)

On balance, we find that Appellant has the better arguments. Provisional Application 60/096,180, the application to which priority is claimed, includes a partial copy of the McLaughlin reference.[3] The Examiner asserts that McLaughlin is "limited to specific ***infusion rates for days 8,[ ]15,[ ]22*** for the dose of ***375[mg]/[m^2] of administered antibody***,"

[2] Declaration of Antonio J. Grillo-Lopez, M.D. under 37 C.F.R. § 1.131 (Mar. 4, 2013) ("Grillo-Lopez Declaration").
[3] Peter McLaughlin, *Rituximab Chimeric Anti-CD20 Monoclonal Antibody Therapy for Relapsed Indolent Lymphoma: Half of Patients Respond to a Four-Dose Treatment Program*, 16 J. CLINICAL ONCOLOGY 2825 (1998) ("McLaughlin"). We note that the copy of McLauglin submitted as part of the provisional application omits the Acknowledgement and References sections and also numbers its pages starting from page one (rather than page 2825). Because the Examiner in his analysis appears to cite to the page numbers of the McLaughlin reference itself rather than to the copy included as part of the provisional application, we do so as well to maintain consistency.

(i.e., "***an infusion rate resulting in mean administration of times of 3.5, 3.3 and 3.3 hours respectively***"), whereas the claims "encompasses any rate faster than 50 mg/h" on days 8, 15, and 22 if no toxicity was seen during the infusion on day 1. (Ans. 3–4.)

We are not persuaded. As Appellant points out, McLaughlin teaches intravenously administering, to patients with relapsed low grade or follicular lymphoma, 375 mg/m^2 of rituximab once a week for a total of four infusions (days 1, 8, 15, and 22), as recited for instance in claim 15. (McLaughlin 2825, right column; 2826, left column.) McLaughlin further teaches that "[t]he initial rate was 50 mg/h, with subsequent infusion rate increase if no toxicity was seen." (*Id.* at 2826, left column.) Moreover, although McLaughlin discloses that in its study actual mean durations of the infusions were 3.5, 3.3, and 3.3 hours, respectively for days 8, 15, and 22 (McLaughlin 2828–2829), the First Levy Declaration[4] explains that a skilled artisan would understand a safe infusion rate to be patient-dependent and thus would not read McLaughlin narrowly as only disclosing these specific infusion rates for days 8, 15, and 22. (First Levy Decl. ¶ 17.)

In light of McLaughlin's general disclosure to increase subsequent infusion rates from the initial rate of 50 mg/h if no toxicity were seen, as well as the discussion in the First Levy Declaration, we disagree with the Examiner that a skilled artisan would understand McLaughlin's disclosure to be limited to the subsequent infusion rates *actually* used in the study (i.e., infusion rates resulting in mean infusion durations of 3.5, 3.3, and 3.3 hours on days 8, 15, and 22).

[4] Declaration of Ronald Levy under 37 C.F.R. § 1.132 (Nov. 22, 2016) ("First Levy Declaration").

In response to the First Levy Declaration, the Examiner emphasized that

> there is no disclosure in ***McLaughlin et al. that the 375[mg]/[m^2] of administered antibody can be delivered at any and all rates faster than 50 mg/h***. For example, the limitation encompass delivery of all of the antibody in 15 minutes or one hour wherein such infusion rates are not disclosed in McLaughlin et al.

(*Id.* at 4.) In short, the Examiner asserts that the provisional application fails to provide a written description of the full scope of the infusion rate claimed (i.e., faster than 50 mg/h).

We are not persuaded because, as discussed above, McLaughlin in fact generally discloses increasing subsequent infusion rates from the initial rate of 50 mg/h if no toxicity were seen, without placing an upper limit on the subsequent infusion rate. (McLaughlin 2826, left column.) To the extent the Examiner is asserting that McLaughlin does not enable a skilled artisan to make or use the full scope of the invention, the Examiner has not provided persuasive evidence contradicting statements in the First Levy Declaration that a skilled artisan would be able to determine the appropriate infusion rate for a given patient in light of McLaughlin's disclosure. *Cf. Capon v. Eshhar*, 418 F.3d 1349, 1359 (Fed. Cir. 2005) ("It is not necessary that every permutation within a generally operable invention be effective in order for an inventor to obtain a generic claim.").

Accordingly, we find that, on the record before us, the claims on appeal are entitled to the priority date of August 11, 1998, the filing date of the '180 provisional application.

Pre-AIA 35 U.S.C. § 102(a)

Because the prescribing information for RITUXAN® cited as prior art by the Examiner is dated November 1997, less than one year before the priority date of August 11, 1998, the prescribing information for RITUXAN® is not prior art under pre-AIA 35 U.S.C. § 102(b). This does not end our inquiry because, under pre-AIA 35 U.S.C. § 102(a), RITUXAN® prescribing information may still be prior art if it predates Appellant's invention of the claimed subject matter.

Under 37 C.F.R. § 1.131, a party may file "an oath or declaration to establish invention of the subject matter of the rejected claim prior to the effective date of the reference." 37 C.F.R. § 1.131(a) (2015). In order to establish such prior invention,

> [t]he showing of facts for an oath or declaration . . . shall be such, in character and weight, as to establish reduction to practice prior to the effective date of the reference, or conception of the invention prior to the effective date of the reference coupled with due diligence from prior to said data to a subsequent reduction to practice.

37 C.F.R. § 1.131(b) (2015). We therefore turn next to a consideration of whether the Grillo-Lopez Declaration[5] shows that the invention of the claimed subject matter antedates the November 1997 prescribing information for RITUXAN®.

We again find that Appellant has the better arguments. Exhibit A of the Grillo-Lopez Declaration is a report dated January 1997, which describes a study conducted at 31 sites the United States and Canada between April 25, 1995 and April 19, 1996. (Grillo-Lopez Decl. ¶¶ 1–2, Ex. A cover page,

[5] Declaration of Antonio J. Grillo-Lopez, M.D. under 37 C.F.R. § 1.131 (Apr. 17, 2017) ("Grillo-Lopez Declaration").

xxv.) The study describes intravenously administering to patients with relapsed low-grade or follicular lymphoma 375 mg/m^2 of IDEC-C2B8 (rituximab) once weekly for four infusions. (*Id.* ¶¶ 2–3, Exhibit A cover page, xxv, 15–16; *see also id.* at Exhibit A 38 (mean administered dose per infusion of 373.5 mg/m^2 (range 23.4–390.6 mg/m^2) including incomplete infusions).) The study states that

> [t]he dose rate for the first IDEC-C2B8 infusion was to be 50 mg/hour for the first hour. If no toxicity was seen, the dose rate was allowed to be escalated in 50 mg increments at 30-minute intervals to a maximum of 300 mg/hour. If the first IDEC-C2B8 dose was well tolerated, the starting flow rate for subsequent infusions was to be 100 mg/hour increasing to a maximum of 400 mg/hour.

(*Id.* at Ex. A 16; *see also id.* ¶¶ 3–4.) The study also states that "some patients required slowing of infusion rate or temporary infusion interruption due to infusion-related adverse events." (*Id.* at Ex. A 38; *see also id.* at Ex. A 16.)

The Examiner has not disputed that the study described in Exhibit A of the Grillo-Lopez Declaration constitutes conception and reduction to practice of the invention of claims 15–17 prior to the effective date of the cited reference (i.e., the November 1997 prescribing information for RITUXAN®). However, the Examiner argues that "the Grillo-Lopez declaration is defective in that it states in paragraph 1 that invention was conceived and reduced to practice in the US whilst page xxv of materials filed in said declaration states that study took place in the US and Canada." (Ans. 9–10.)

We are not persuaded. Although Dr. Grillo-Lopez does not specifically state that part of the study took place in Canada, we do not find the statement in his declaration to be inaccurate because part of the study

also took place in the United States. (Grillo-Lopez Decl. Ex. A xxv (study took place in 31 sites in the United States and Canada).) Furthermore, Canada is a NAFTA country. 37 C.F.R. § 1.131(a) permits prior invention to be established in a non-U.S. NAFTA country after December 8, 1993, and the study at issue took place after that date. (*Id.* (study took place between April 25, 1995 and April 19, 1996).)

Accordingly, we reverse the Examiner's rejection of claims 15–17 as anticipated by the November 1997 prescribing information for RITUXAN®.

II.

Issue

The Examiner has rejected claims 15–17 as obvious over FDA Transcript. The Examiner finds that the FDA Transcript teaches all of the limitations of the claims except that it does not specifically teach that "the initial infusion rate [for rituximab] on day 8, 15, 22 was greater than 50 mg/hour if no toxicity was seen on day 1." (Ans. 6.) However, the Examiner finds that a skilled artisan would have been motivated to practice the claimed method with a reasonable expectation of success, because "increasing the infusion rate results in a faster treatment for the patient" and the FDA Transcript teaches that "the antibody is administered at an initial intravenous rate of 50 mg/hour and increased to a maximal rate of 150 mg/hour **wherein the majority of adverse events occur with the first infusion**." (*Id.* at 6–7.)

Appellant contends that the FDA Transcript is not a printed publication within the meaning of 35 U.S.C. § 102(a) or § 102(b), or a public use within the meaning of 35 U.S.C. § 102(b). (Appeal Br. 24; Reply

Br. 5–8.[6]) Appellant also contends that the FDA Transcript does not provide "motivation or reasonable expectation of success that an initial infusion rate faster than 50 mg/h for the infusions on days 8, 15, or 22 should be tried, much less that it would be safe and effective." (Appeal Br. 20.)

Appellant does not separately argue the claims. We therefore limit our analysis to claim 15 as representative. The issues with respect to this rejection are (1) whether the FDA Transcript is a printed publication or a public use within the meaning of 35 U.S.C. § 102 (b)[7] and if so, (2) whether, based on the FDA Transcript, a skilled artisan would have had reason to treat patients with rituximab using an initial infusion rate of greater than 50 mg/hour on day 8, 15, and 22 if no toxicity was seen on day 1 of treatment.

Analysis

We agree with the Examiner that the FDA Transcript renders claim 15 obvious.

Whether the FDA Transcript Is Prior Art

As explained by our reviewing court, the key inquiry is whether the FDA Transcript was made "sufficiently accessible to the public interested in the art" before the critical date, which is August 11, 1997 in this case for purposes of 35 U.S.C. § 102(b). *Constant v. Advanced Micro-Devices, Inc.*, 848 F.2d 1560, 1568 (Fed. Cir. 1988). "A given reference is 'publicly

[6] Appellant's Reply Brief does not include page numbers. Therefore, we refer to page numbers in the Reply Brief as if the Reply Brief was numbered sequentially starting with the first page.

[7] Appellant has argued that the FDA Transcript is not a printed publication under either 35 U.S.C. § 102(a) or § 102(b). Because similar legal analysis applies in both cases, and because 35 U.S.C. § 102(a) allows Appellant to "swear behind" the FDA Transcript, we focus our analysis on whether the FDA Transcript is a printed publication under 35 U.S.C. § 102(b).

accessible' upon a satisfactory showing that such document has been disseminated or otherwise made available to the extent that persons interested and ordinarily skilled in the subject matter or art exercising reasonable diligence, can locate it." *Bruckelmyer v. Ground Heaters, Inc.*, 445 F.3d 1374, 1378 (Fed. Cir. 2006). "Whether a reference is publicly accessible is determined on a case-by-case basis based on the 'facts and circumstances surrounding the reference's disclosure to members of the public.'" *Voter Verified, Inc., v. Premier Election Solutions, Inc.*, 698 F.3d 1374, 1380 (Fed. Cir. 2012) (quoting *In re Lister*, 583 F.3d 1307, 1311 (Fed. Cir. 2009)). Bearing the above principles in mind, we find that the FDA Transcript is a printed publication within the meaning of 35 U.S.C. § 102(b), as further discussed below.

Appellant contends that "[t]he Examiner offers no evidence that the [FDA] Transcript was ever actually disseminated before the priority date." (Reply Br. 5.) We are not persuaded. We find that the evidence supports the conclusion that the FDA Transcript was made available to the public prior to the critical date. In particular, Appellant cites to the Board's decision denying institution in IPR2017-01094[8] to argue that the FDA Transcript is not a printed publication. (Appeal Br. 24.) That decision refers to an August 26, 2016 letter from Dynna Bigby ("Bigby Letter"),[9] which explains that, based on procedures in place in 1997, FDA's Division of

[8] *Celltrion, Inc. v. Biogen, Inc.*, IPR2017-01094, Paper No. 12 (Oct. 2, 2017).
[9] *Celltrion, Inc. v. Biogen, Inc.*, IPR2017-01094, Ex. 1039. Ms. Bigby is a Supervisory Administrative Proceedings Officer at the Division of Dockets Management ("DDM") at the FDA/Office of the Executive Secretariat. (Bigby Letter 001.)

Dockets Management ("DDM") would have received the FDA Transcript on Aug. 8, 1997, the date stamped on the transcript. (Bigby Letter 001.) The Bigby Letter further states that, "[in] 1997, once the DDM received a document, it [would have] made that document publicly available via the DDM Public Reading Room." (*Id.*) The Bigby Letter concludes that, therefore, "[f]ollowing August 8, 1997, any member of the public could have requested and received a copy of the transcript in question by filling out a reading room request form."[10] (*Id.*) Appellant has not persuasively disputed any of the facts recited in the Bigby Letter. Accordingly, we find a prima facie case exists that the FDA Transcript was disseminated or otherwise made available before the critical date of August 11, 1997.

We next turn to the question of whether the FDA Transcript was made available *to a sufficient extent* to render it a printed publication within the meaning of § 102(b). Appellant relies on the reasoning articulated in the Board's decision denying institution of IPR2017-01094, which found that the petitioner in that case failed to provide "'some supported explanation that . . . availability of the FDA Transcript was in a manner and to an extent that 'persons interested and ordinarily skilled in the subject matter or art exercising 'reasonable diligence' would have been able to locate it,'" and contends that the FDA Transcript was not "publicly accessible" to the extent required to establish it as a "printed publication" within the meaning of

[10] To the extent Appellant's argument is that there is no evidence a member of the public actually accessed the document, we are not persuaded. There is no requirement that a reference be actually accessed by a member of the public to be a printed publication, so long as it was "disseminated or otherwise made available" to the extent that an interested and ordinarily skilled person can locate it by exercising reasonable diligence. *Bruckelmyer v. Ground Heaters, Inc.*, 445 F.3d 1374, 1378 (Fed. Cir. 2006).

35 U.S.C. § 102(b). (Appeal Br. 24; Reply Br. 5–6.[11])

We are not persuaded. As the Examiner points out, the transcript relates to a public meeting of FDA's Biological Response Modifiers Advisory Committee, publicly announced via the Federal Register, at which members of the public were invited to speak. (Ans. 12; FDA Tr. 7:21–8:2.) The Notice of Meeting in the Federal Register explicitly explained that the meeting relates to "Rituximab (C2B8 monoclonal antibody), IDEC" and that IDEC "is seeking an indication for Rituximab as treatment for patients with relapsed or refractory low grade or follicular B-cell non-Hodgkin's Lymphoma." 62 Fed. Reg. 32619 (1997).

Furthermore, the Notice of Meeting explained that the notice is "given under the Federal Advisory Committee Act (5 U.S.C. app. 2)." *Id.* The Federal Advisory Committee Act (FACA) states that, other than for national security reasons, "timely notice of each [advisory committee] meeting shall be published in the Federal Register, and the Administrator shall prescribe regulations to provide for other types of public notice to insure that all interested persons are notified of such meeting prior thereto." Federal Advisory Committee Act, 5 U.S.C. App 2 § 10(a)(2).

Given FACA's intent to provide notice of advisory committee meetings to "all interested persons," and given that an interested member of the public unaffiliated with the sponsor of rituximab in fact spoke at the meeting pursuant to the Federal Register notice (FDA Tr. 7:23–8:9, 15:6–10), we find a prima facie case exists that an ordinarily skilled artisan for

[11] Appellant's Reply Brief does not include page numbers. Therefore, we refer to page numbers in the Reply Brief as if the Reply Brief was numbered sequentially starting with the first page.

purposes of the claimed invention (e.g., an oncologist or a medical researcher of average experience) would have been aware of the Biological Response Modifiers Advisory Committee meeting regarding rituximab.

As to the public accessibility of the *transcript*, we note that FACA states that, "[e]xcept where prohibited by contractual agreements entered into prior to the effective date of this Act, agencies and advisory committees shall make available to any person, at actual cost of duplication, copies of transcripts of agency proceedings or advisory committee meetings." *Id.* at § 11(a). FACA additionally states:

> (b) Subject to section 552 of Title 5, United States Code, the records, reports, transcripts, minutes, appendixes, working papers, drafts, studies, agenda, or other documents which were made available to or prepared for or by each advisory committee *shall be available for public inspection and copying at a single location in the offices of the advisory committee or the agency to which the advisory committee reports* until the advisory committee ceases to exist.
>
> (c) Detailed minutes of each meeting of each advisory committee shall be kept and shall contain a record of the persons present, a complete and accurate description of matters discussed and conclusions reached, and copies of all reports received, issued, or approved by the advisory committee. The accuracy of all minutes shall be certified to by the chairman of the advisory committee.

Id. at §§ 10(b)–(c) (emphasis added).

In short, there is evidence that an FDA advisory committee meeting about rituximab was advertised in the Federal Register in June 2016, that a meeting was held in July 1997, that a transcript of the meeting was generated and was available to the public in the FDA reading room by August 8, 1997, prior to the critical date, and that there is a reasonable

expectation, if not a legal requirement, that transcripts of FDA advisory committee meetings would be publicly available at a designated place at the agency. We find based on the above that there is sufficient evidence that an interested and ordinarily skilled artisan would have been able to locate the FDA Transcript through the exercise of reasonable diligence more than one year before the critical date, such that the burden is shifted to Appellant to demonstrate that the transcript was *not* available to or accessible by the public to a sufficient extent. Appellant has provided no persuasive evidence to this effect. Accordingly, we agree with the Examiner that the FDA Transcript was a printed publication for purposes of 35 U.S.C. § 102(b).[12]

Motivation to Combine and Reasonable Expectation of Success

Appellants argue that, even if the FDA Transcript were a printed publication, the FDA Transcript "would not have motivated [a person of ordinary skill in the art] to increase the initial infusion rate of subsequent infusions on days 8, 15, and 22 above 50 mg/h" rather than using the same

[12] We acknowledge that the panel in IPR2017-01094 found that petitioner had not shown that the FDA Transcript was a printed publication. In that case, however, Petitioner did not cite to publication of the Notice of Hearing in the Federal Register, attendance of the hearing by an interested member of the public pursuant to the notice, or the requirements of FACA in support of the public accessibility of the FDA Transcript. These arguments were thus not before the panel in IPR2017-01094 and were not discussed in the panel's decision denying institution. As discussed, we find that evidence, including the evidence cited above, suffices to establish a prima facie case that the FDA Transcript is a printed publication within the meaning of § 102(b). Appellant has not provided persuasive countervailing evidence that a skilled artisan would not be able to locate the FDA Transcript using reasonable diligence. Accordingly, on review of the entirety of record we find that a preponderance of evidence supports the finding that the FDA Transcript is a printed publication.

50 mg/h rate for the infusions on each of days 1, 8, 15, and 22. (Appeal Br. 20.)

We are not persuaded. The FDA Transcript teaches administering rituximab to treat patients with relapsed or refractory low-grade or follicular B-cell non-Hodgkin's lymphoma, where rituximab is administered at 375 mg/m^2 by intravenous infusion given once weekly times four. (*See, e.g.*, FDA Transcript 16:15–18, 18:16–21, 35:19–25, 36:20–24, 79:1–4, and 87:23–88:2.) Moreover, while the FDA Transcript does not specifically teach treating patients with rituximab using an initial infusion rate of greater than 50 mg/hour on day 8, 15, 22 if no toxicity was seen on day 1 of treatment, it teaches that rituximab was "administered . . . at an initial intravenous rate of 50 mg/hour and increased to a maximal rate of 150 mg/hour" and that "the majority of the adverse events . . . occur with the first infusion, and subsequent infusions are characterized by much lower incidence of adverse events." (FDA Tr. 29:5–8, 13–14; 32:23–33:3; 86:16–22, and 91:10–13.) The Examiner asserts that, in light of the above, the limitation regarding increasing the infusion rate during subsequent infusions would have been obvious to a skilled artisan because "increasing the infusion rate results in a faster treatment for the patient." (Ans. 6–7.)

We agree that the Examiner has established a prima facie case of obviousness with respect to the limitation. As our reviewing court has explained

> an implicit motivation to combine exists not only when a suggestion may be gleaned from the prior art as a whole, but when the "improvement" is technology-independent and the combination of references results in a product or process that is more desirable, for example because it is stronger, cheaper, cleaner, faster, lighter, smaller, more durable, or more efficient.

> Because the desire to enhance commercial opportunities by improving a product or process is universal—and even common-sensical— . . . there exists in these situations a motivation to combine prior art references even absent any hint of suggestion in the references themselves. In such situations, the proper question is whether the ordinary artisan possesses knowledge and skills rendering him *capable* of combining the prior art references.

Dystar Textilfarben Gmbh & Co. Deutschland KG v. C.H. Patrick Co., 464 F.3d 1356, 1368 (Fed. Cir. 2006). Here, the Examiner has explained that a faster infusion rate would result in a faster (and presumably more efficient) treatment process for the patient. Likewise, because the FDA Transcript explicitly teaches infusion rates of up to 150 mg/hr and that most of the adverse events occur during the first infusion, the evidence supports a finding that a skilled artisan would be capable of combining the teachings in the FDA Transcript to begin the infusion rate at 50 mg/hr but increase the infusion rate during subsequent infusions.

Appellant relies largely on the Second Levy Declaration[13] in arguing that the FDA Transcript would not have provided a motivation or reasonable expectation of success in arriving at the claimed invention. In his declaration, Dr. Levy states that a skilled artisan at the time of invention would have understood that (1) "infusion reactions can occur with rituximab infusions"; (2) "[h]igher infusion speeds increase the risk of the adverse events because more rituximab is present in the body . . . in a shorter window of time"; and (3) "a severe infusion-related adverse event cause[d]

[13] Declaration of Ronald Levy under 37 C.F.R. § 1.132 (April 11, 2017) ("Second Levy Declaration").

by adaptive immunity is more likely to occur in subsequent infusions compared to the first infusion." (Second Levy Decl. ¶¶ 7–12.)

Dr. Levy states that, in fact, in the rituximab clinical trials some patients had adverse events on subsequent infusions without having had an adverse event in during the first infusion, and prescribing information for other therapeutic antibodies at the time of the invention allowed rate increase during the first infusion while the initial rate remained constant for subsequent infusions. (*Id.* ¶¶ 13, 15.) Accordingly, Dr. Levy opined that, because "much was still unknown about the safety of rituximab infusions," a skilled artisan "would not [have been] motivated or have [had] a reasonable expectation of safety for starting rituximab infusion rates faster in subsequent infusions," and "the FDA Transcript disclosure that the rate of infusion was increased during the course of each infusion and fewer adverse events were seen with subsequent infusions would not render obvious the inventive concept that rituximab could be infused at a higher initial rate on subsequent infusions." (*Id.* ¶¶ 14, 16.)

We are not persuaded. As an initial matter, in the First Levy Declaration Dr. Levy explained that a skilled artisan would have understood McLaughlin's disclosure that "[t]he initial infusion rate was 50 mg/h, with subsequent infusion rate increase if no toxicity was seen" to mean that infusion rate was increased in *subsequent* infusions rather than that the infusion rate was increased during the course of *each* infusion. (First Levy Decl. ¶ 11.) Dr. Levy does not explain why a skilled artisan would read the FDA Transcript's disclosure of increasing infusion rate differently, i.e., that

the rate was increased during the course of each infusion rather than increased in subsequent infusions.[14]

Furthermore, even assuming that the FDA Transcript only disclosed increasing infusion rate during the course of each infusion, "[o]nly a reasonable expectation of success, not absolute predictability, is necessary for a conclusion of obviousness." *In re Longi*, 759 F.2d 887, 897 (Fed. Cir. 1985). Likewise, "a given course of action often has simultaneous advantages and disadvantages, and this does not necessarily obviate motivation to combine." *Medichem, S.A. v. Rolabo S.L.,* 437 F.3d 1157, 1165 (Fed. Cir. 2006). Rather, "'the benefits, both lost and gained, should be weighed against one another.'" *Id.* (quoting *Winner Int'l Royalty Corp. v. Wang*, 202 F.3d 1340, 1349 n.8 (Fed. Cir. 2000)). For instance, although the FDA Transcript describes various adverse events that occurred with treatment using rituximab, the Biological Response Modifiers Advisory Committee was unanimous in finding the risks of rituximab therapy to be acceptable given the efficacy data. (FDA Tr. 104:14–23.)

In this case, while we acknowledge Dr. Levy's statement that higher infusion rate generally increase the likelihood of adverse events, the FDA Transcript teaches administering rituximab at an infusion rate as high as 150

[14] Appellant cites to paragraph 6 of the Second Levy Declaration as support that "the FDA Transcript teaches that the initial infusion rate remained 50 mg/hour on the subsequent infusions." (Appeal Br. 22.) The only evidence that Dr. Levy cites to for support of this statement, however, is the Examiner's February 22, 2017 Non-Final Rejection ("Non-Final Act."). (Second Levy Decl. ¶ 6.) We note that the Examiner did not state that "the FDA Transcript teaches that the initial infusion rate remained 50 mg/hour on the subsequent infusions," merely that the FDA Transcript "does not *specifically* teach that the initial infusion rate on days 8, 15, 22 was greater than 50 mg/hour." (Non-Final Act. 5 (emphasis added).)

mg/hour without teaching that increasing the infusion rate resulted in unacceptable safety concerns. Indeed, the FDA Transcript teaches that rituximab "is safe with limited adverse events." (FDA Tr. 25:10.) Likewise, although we acknowledge Dr. Levy's statement that certain types of adverse events are more likely in subsequent infusions than the initial infusion, the FDA Transcript teaches that, at least with respect to rituximab, most of the adverse events occurred during the initial infusion. Finally, while Dr. Levy cites to prescription information relating to other therapeutic antibodies that increased the rate during a first infusion but does not start a subsequent infusion at a higher initial infusion rate, Dr. Levy does not provide a persuasive explanation as to why this renders alternative administration schedule for rituximab non-obvious, given the specific teachings in the FDA Transcript regarding rituximab. Indeed, the evidence would appear to support a conclusion that infusion rate is a known result-effective variable, and "discovery of an optimum value of a result effective variable in a known process is ordinarily within the skill of the art." *In re Boesch*, 617 F.2d 272, 276 (CCPA 1980).

In short, taking all of the evidence into account, we are not persuaded by Dr. Levy's conclusion that "the FDA Transcript[']s disclosure that the rate of infusion was increased during the course of each infusion and fewer adverse events were seen with subsequent infusions would not render obvious the inventive concept that rituximab could be infused at a higher initial rate on subsequent infusions." (Second Levy Decl. ¶ 16.)

Accordingly, we affirm the Examiner's rejection of claims 15–17 as obvious over the FDA Transcript. Because we rely on evidence not

expressly recited by the Examiner, however, we designate the affirmance as a new ground of rejection.

SUMMARY

In summary, we reverse the Examiner's rejection of claims 15–17 as anticipated by the November 1997 prescribing information for RITUXAN®.

We affirm the Examiner's rejection of claims 15–17 as obvious over the FDA Transcript but designate our affirmance as a new ground of rejection.

TIME PERIOD FOR RESPONSE

This decision contains a new ground of rejection pursuant to 37 C.F.R. § 41.50(b). Section 41.50(b) provides "[a] new ground of rejection pursuant to this paragraph shall not be considered final for judicial review." Section 41.50(b) also provides:

> When the Board enters such a non-final decision, the appellant, within two months from the date of the decision, must exercise one of the following two options with respect to the new ground of rejection to avoid termination of the appeal as to the rejected claims:
>
> (1) *Reopen prosecution*. Submit an appropriate amendment of the claims so rejected or new Evidence relating to the claims so rejected, or both, and have the matter reconsidered by the examiner, in which event the prosecution will be remanded to the examiner. The new ground of rejection is binding upon the examiner unless an amendment or new Evidence not previously of Record is made which, in the opinion of the examiner, overcomes the new ground of rejection designated in the decision. Should the examiner reject the claims, appellant may again appeal to the Board pursuant to this subpart.

> (2) *Request rehearing*. Request that the proceeding be reheard under § 41.52 by the Board upon the same Record. The request for rehearing must address any new ground of rejection and state with particularity the points believed to have been misapprehended or overlooked in entering the new ground of rejection and also state all other grounds upon which rehearing is sought.

Further guidance on responding to a new ground of rejection can be found in the Manual of Patent Examining Procedure § 1214.01.

No time period for taking subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED; 37 C.F.R. § 41.50(b)